Restoring Ureagenesis in Hepatocytes by CRISPR/Cas9-mediated Genomic Addition to Arginase-deficient Induced Pluripotent Stem Cells.

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Public Summary:
Urea cycle disorders are incurable enzyme defects that affect nitrogen metabolism and typically lead to elevated nitrogen. Arginase deficiency results from a mutation in the arginase 1 gene, typically results in developmental disabilities, seizures, spastic diplegia, and sometimes death. Current medical treatments for urea cycle disorders are only marginally effective, with some being treated by liver transplantation which is effective but limited by graft availability. Advances in human induced pluripotent stem cell research has allowed for the genetic modification of stem cells for cell transplantation. In this study, we demonstrate a universally-applicable gene editing strategy utilizing the hypoxanthine-guanine phosphoribosyltransferase gene to genetically modify and restore arginase activity in genetically distinct patient-specific human induced pluripotent stem cells and liver cell derivatives. Successful strategies restoring gene function in patient-specific human induced pluripotent stem cells may advance applications of genetically modified cell therapy to treat urea cycle and other inborn errors of metabolism.

Scientific Abstract:
Urea cycle disorders are incurable enzymopathies that affect nitrogen metabolism and typically lead to hyperammonemia. Arginase deficiency results from a mutation in Arg1, the enzyme regulating the final step of ureagenesis and typically results in developmental disabilities, seizures, spastic diplegia, and sometimes death. Current medical treatments for urea cycle disorders are only marginally effective, and for proximal disorders, liver transplantation is effective but limited by graft availability. Advances in human induced pluripotent stem cell research has allowed for the genetic modification of stem cells for potential cellular replacement therapies. In this study, we demonstrate a universally-applicable CRISPR/Cas9-based strategy utilizing exon 1 of the hypoxanthine-guanine phosphoribosyltransferase locus to genetically modify and restore arginase activity, and thus ureagenesis, in genetically distinct patient-specific human induced pluripotent stem cells and hepatocyte-like derivatives. Successful strategies restoring gene function in patient-specific human induced pluripotent stem cells may advance applications of genetically modified cell therapy to treat urea cycle and other inborn errors of metabolism.